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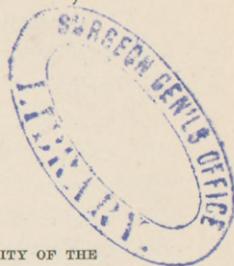
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ON PIGMENTARY DEPOSITS IN THE BRAIN,
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THAT the agent which, for want of a better name, we call malaria, is capable of making a profound impression upon the nervous systems of those upon whom its toxic influence is exerted, has long been known, and is so generally admitted at the present time that no argument is necessary to enforce the fact upon the medical profession. Indeed, it is contended by many able writers that the primary manifestations of malarial poisoning which we witness every day are in reality evidence of disease of the nervous system.

My object, however, in this memoir, is not to discuss the question of the pathology of malarial fevers, but to call attention to a very remarkable condition of the brain, the result of such fevers, and which, though hitherto not altogether ignored, has scarcely obtained that consideration which its importance demands. This is the deposition of pigment in the brain, either in the form of emboli obstructing the smaller vessels and the capillaries suddenly; or of thrombi, the pigment being slowly deposited along the inner wall of the vessels and thus gradually leading to their occlusion; or as a transudation into the perivascular tissue.

The condition has ordinarily been spoken of by the few authors who have mentioned it as embolism, but I think it will be admitted, from a consideration of the facts and arguments I have to adduce, that both the other forms of pigmentary

deposit are possible. Indeed, Feltz* goes so far as to deny the existence of pigmentary embolism, asserting that the deposits are always slowly made from the blood, and the vessels thus gradually occluded.

According to Virchow,† Dr. Stiebel was the first to notice the occurrence of pigment-cells in the blood. Meckel ‡ appears to have been the first to call attention to their presence in this fluid in connection with malarial poisoning and hypertrophy of the spleen, and Virchow§ discovered numerous pigment-cells in the blood and the enlarged spleen of a man who became dropsical after a persistent intermittent fever.

Previous, however, to these observations, the fact of pigment existing abnormally in various organs of the body had been noticed. Frerichs|| refers to several statements to that effect, and among others to the case described by Stoll, in which there was a dark pigmentary deposit in the brain and liver of a woman who had died after several attacks of fever. It appears also that black pigmentary deposits were repeatedly observed in the spleen, liver, and brain during the fever epidemic which, in 1826, raged along the coast of the North Sea.

In 1831, Bright¶ described and figured the brain of a man who had died from cerebral paralysis, which appeared to have resulted from an attack of fever. The cortical substance was of a dark color, like black-lead. In this country, Dr. Stewardson,** of Philadelphia, has noticed the dark color of the spleen in the cases of individuals who had died from malarial fevers.

In cases of malanæmia and pigment-liver, resulting from malarial poisoning, the pigment would appear to be separated from the blood in the first place in the spleen, and to re-

* *Traité clinique et expérimentale des embolies capillaires*, Paris, 1870, p. 223.

† *Die Cellularpathologie*, Vierte Auflage, Berlin, 1871, p. 263.

‡ *Zeitschrift für Psychiatrie*, 1847.

§ Quoted by Frerichs from Virchow's *Archiv für patholog. Anatomie*, 1847.

¶ *A Clinical Treatise on Diseases of the Liver*, New Sydenham Society Translation, vol. i. p. 314 et seq.

¶ Reports of Medical Cases, London.

** *American Journal of the Medical Sciences*, April, 1841.

enter the circulation as masses of amorphous pigment and as pigment-holding cells. From this organ it is carried to distant parts of the body, and can be most readily detected in the brain by the dark color which it gives to the cerebral substance, especially the cortical layer, in the vessels of which, it seems most disposed to accumulate. The tinge is usually that of chocolate or black-lead. Unless the quantity be very great, the white tissue is unchanged in appearance; but when present in excessive amount, this latter is rendered gray, and the smaller vessels resemble brown streaks. Microscopic examination shows the capillaries to be filled with black granules and scales, which sometimes are uniformly distributed, and at others are collected in groups.*

In regard to this matter, Frerichs † makes the following remarks:

“The next organ in point of frequency to the liver which undergoes important organic and functional derangement is the brain. Numerous particles of pigment which have passed unarrested through the vessels of the liver and the lungs accumulate in the narrow capillaries of this organ, and especially in those of the cortical substance. Even by simple inspection of the shade of color, we can form an approximate notion of the quantity of coloring matter which has been deposited, and of the extent of the vascular obstruction. We must not, however, rely entirely on inspection; for slight accumulations of pigment in the capillaries easily escape notice, particularly when viewed with the unaided eye, and can only be distinguished with the assistance of the microscope. In addition to the above, it is not at all uncommon for the vessels to become obstructed by a colorless fibrinous-like coagulum, which, of course, does not affect the shade of color. The mechanical interruption to the circulation which is produced in this way, not unfrequently gives rise to rupture of the small vessels, and the formation of numerous capillary apoplexies. Meckel long ago made observations of this nature. Planer described eight cases in which small extravasations were scattered through the gray and white substance of the

* Frerichs, op. cit. p. 319.

† Op. cit. p. 326.

brain. These numerous hemorrhages have not come under my own observation, but in two cases I have observed extravasation into the meninges.

“It has not been proved by direct examination whether, besides hemorrhages, other organic lesions of the brain, such as atrophy from interrupted supply of plasma, result from occlusion of the capillaries.

“I have seen pigment brains of old date without any remarkable diminution of the cortical substance. Other functional derangements indicative of organic changes in the cortical substance of the brain have only occurred to me in three cases. These cases, however, I only saw in a cursory manner during a journey in Poland.”

This extract sums up what was known of the subject fifteen years ago.

The occurrence of head symptoms after attacks of intermittent fever was observed by Sydenham,* who called attention to the fact that mental derangement was sometimes a sequence of such an affection, and that under the use of depleting measures the patients soon passed into a state of imbecility. But, as a rule, the fact seems to have escaped notice, the only circumstance generally referred to as regards cerebral disturbance being that which takes place during the paroxysm, and which, of course, is not directly related to the matter now under notice.

In an interesting memoir read before the French Academy of Medicine, Itard † cites several cases in support of the opinion that inflammatory affections of the brain are sometimes the cause of intermittent fever; but so far from sustaining this view they rather go to show that very marked cerebral disturbance may result as a consequence of repeated attacks of fever. He quotes a case from Comparettii, which is so apposite to the subject of this paper that I am induced to refer to it with some fullness of detail.

A man aged thirty-four, after great fatigue of mind and

* Opera Omnia, Sydenham Society Edition, Sect. 1, Cap. v.

† Mémoire sur quelques phlegmasies cérébrales, présentées comme cause de fièvres intermittentes pernicieuses. Mémoires de l'Académie Royale de Médecine, t. i. 1828, p. 19.

body, was attacked at Venice, in the spring of 1771, with a tertian fever, which reappeared at the same time the two following years, and which was cured each time by purgatives and bark.

In the spring of 1774, the fever recurred, and this time under the form of a double tertian. It was treated with leeches, purgatives, general bloodletting, and with bark, the latter succeeding best, but not being sufficient to accomplish a perfect cure; for at the end of a few weeks the accessions reappeared, and always with the accompaniment of violent headache, more severe on the right side of the head, and especially intense in the auditory canal, from which it appeared to radiate to the lower jaw. With this pain there were deafness and tinnitus of the corresponding ear, a painful feeling of constriction about the neck, great prostration, a sense of weakness of all the senses, dullness of the intellectual faculties, and the impossibility of supporting the least noise or the feeblest light without intense suffering. During one of the more violent accessions, which occurred in the month of October, there were, besides these symptoms, a protracted syncope followed by stupor and tetanic convulsions. After a slight amendment, obtained by larger doses of quinine, the fever reappeared with all the old cerebral manifestations in even greater intensity. The pain in the head was of the most agonizing character and out of all proportion to the severity of the fever. The patient complained of a feeling of distention in the membranes of the brain, of fullness in the whole head, and of a tenderness of the scalp which caused the least touch to result in intense pain. Besides the deafness, the eyesight was weakened. The light of a candle appeared to be surrounded by a bluish zone, and there were oscillations of the pupils without change in the intensity of the light. The pain in the ear became more severe, and then it was noticed that there was a purulent discharge from the meatus. Close examination revealed the existence of a little white tumor, terminated by a black point, and situated deep in the auditory canal. Although it is not so stated, it is presumed that this tumor was removed or was discharged in some way; for from

this time the patient began to recover, and was soon entirely well.

Of the two cases referred to by Frerichs, and to which allusion has already been made, one was that of a lady in her fortieth year, who, after an attack of quotidian fever, accompanied by somnolence, suffered from protracted loss of memory. The headache and giddiness which were present gradually diminished; but the weakness of memory, and the inability to find suitable words for objects and ideas, were still on the increase two months after the cessation of the ague.

The other case was that of a young girl, nine years old, whose mental powers had been good, but who, suffering from several attacks of intermittent fever, lost the use of her intellectual faculties, and lapsed into a state of complete idiocy.

In relation to these cases, Frerichs remarks that it is uncertain whether atrophy of the brain had resulted from occlusion of the capillaries, or whether it had been induced by the extensive capillary aneurisms consequent on this occlusion, or whether the intermittent fever was complicated with other accidental changes in the brain.

Meckel's case, also previously alluded to, was that of a lunatic, and here the post-mortem examination showed the existence of an enlarged and pigmented spleen.

The effect of repeated attacks of intermittent fever upon the mental faculties has doubtless been noticed by all who have had occasion to observe the inhabitants of malarious regions. Maccullaugh,* many years ago, graphically described the condition. After calling attention to the bodily degeneration of the residents of the South of France, as induced by malarial fevers, he says,

“The condition of the mental faculties, whether intellectual or moral, is scarcely less remarkable while it is more interesting; and if there should appear any exaggeration as to some particulars, or should any special fact, as asserted, depend on collateral causes of another nature, the general bearing of the whole, as related of Italy and France, has been confirmed too often by remarks of a similar nature made in America and

* Malaria. An Essay on the Production and Propagation of this Poison, etc., London, 1827, p. 433.

elsewhere by competent observers, to leave any doubt as to the leading circumstances.

“That apathy which was just noticed as expressed in the physiognomy is a character which influences the whole conduct of these degraded and unfortunate beings, often proceeding to such a degree that they are scarcely elevated above the beasts in point of feeling—seeking solitude, shunning society and amusements alike; without affection, without interest in any thing, they make no exertion to better their condition; not even to avoid the sources of danger which surround them, or to take the most common precautions which are pointed out; while attached to the soil from habit or indolence, rather than from regard, they will not be convinced of its nature or dangers; fatalists in practice, and even in belief, and refusing to admit that there is any other lot in life than that which they call their own.

“That the general intellectual faculties are degraded is a universal remark; while in many places, and very notably in the Maremma of Tuscany, it is observed that absolute idiotism is common.”

He also mentions the fact that among the diseases induced by malarial fevers, apoplexy and paralysis are common, as well as headache, neuralgia, sciatica, and other affections of the nervous system.

Among the more recent writers who have considered the subject of pigmentary cerebral embolism, Jaccoud* expresses his belief that pigment, either in the form of being contained in cells, or as free granules, may enter the blood from the spleen or liver and obstruct the cerebral capillaries, especially those of the gray matter. While doubting whether there are any pathognomonic symptoms of the affection, he states that the phenomena are headache, hallucinations, delirium, and convulsions, followed by coma more or less profound. Paralysis is rare, but may be either of the hemiplegic or paraplegic form. These symptoms are only significant of the exact pathological condition when there is the history of intermittent fever and of splenic hypertrophy. His knowledge does not appear to be personal, but to be based upon the observations of

* *Traité de pathologie interne*, t. i., Paris, 1870, p. 144.

Meckel, Heschl, Planer, Frerichs, Virchow, Duchek, and Grohe.

In their text-books on the practice of medicine, Drs. Flint* and Aitken† mention the fact, on the authority of Virchow and Frerichs, that in malanæmia the pigment may obstruct the capillaries of the brain and give rise to certain cerebral symptoms.

Bennet,‡ though referring to the subject of blood-pigments and their pathology, does not mention the circumstance that the brain may be diseased by black pigment obstructing its vessels, nor does he seem to be aware of the relation existing between this pigment and malarial fevers, and hypertrophy of the spleen.

Many years ago, my attention, while residing in malarious regions, was directed to the fact that not a few persons who had suffered from repeated attacks of the endemic fevers, and who were, at the same time, subject to enlargement of the spleen, exhibited evidences of cerebral disease, such as have been already mentioned. But it is only recently that I have succeeded in establishing the relation during the lifetime of the patient, and that I have demonstrated the truth of my views by experiments on living animals. To the consideration of these observations and experiments, I now ask the attention of the Association.

CASE I.—N. B. consulted me at the suggestion of my friend, Dr. L. Weber, February 26th, 1874. On inquiry and examination, I found that he was absolutely deaf in both ears, that he had severe pains in the head, and that he was subject to frequent attacks of epileptic convulsions. It also appeared that he had for several years suffered from intermittent fever, and was then living in a malarious part of the city (Harlem), and had occasional paroxysms.

Examination of the ears revealed no abnormal condition, and I accepted the views of Profs. Knapp and Roosa, who had

* A Treatise on the Principles and Practice of Medicine, Philadelphia, 1868, pp. 95, 854, 872.

† The Science and Practice of Medicine, Philadelphia, 1872, p. 127.

‡ Clinical Lectures on the Principles and Practice of Medicine. Third edition. Edinburgh, 1859, p. 243, *et seq.*

seen the case (for deafness only), had diagnosticated disease of the internal ear, and had given an unfavorable prognosis. Ophthalmoscopic examination showed the existence of double optic neuritis, with pigmentary deposits mainly at the outer periphery of the retina. Both optic papillæ were deformed.

I gave an unfavorable prognosis, and not at that time recognizing the malarious element in the case, treated the patient with the bromide and iodide of potassium. On the 26th of February, he again visited me. There were no marked signs of improvement, and I directed the medicines to be continued. In addition, however, I prescribed arsenic, in the form of Fowler's solution—five drops to be taken three times a day. On examining the abdomen, I discovered a considerable degree of splenic hypertrophy, and it was this, conjoined with the fact that he was still having an attack of intermittent fever every seventh day, which induced me to prescribe arsenic; quinine had already been taken in extreme doses without effect.

From this time, he began to improve; the pain ceased in a few days; and in about a week the epileptic seizures were arrested; he had no further paroxysms of intermittent fever.

I continued the treatment, and about a month after he first came under my charge, his brother and sister hurried to my residence late one night to tell me that their brother's hearing had suddenly returned in one ear. The next day, the other ear reacquired its full hearing power. He had been entirely deaf for over two years.

I have repeatedly seen this patient since. He remains well in every respect, though he occasionally takes the arsenic for a week or two at a time. His case is alluded to by my friend, Prof. Roosa, in an interesting paper upon the relation of disease of the internal ear to disease of the brain. Prof. Roosa has seen the patient, and has satisfied himself of the entire restoration.

Last winter, the patient visited me, and I made a renewed examination. The neuro-retinitis still existed; the papillæ were still deformed; but vision was not materially impaired. The pigmentation was present, but the spots were modified in form, smaller and more rounded, as if the larger masses had been broken up into smaller ones. The spleen was very much

reduced in size. Holding it firmly against the anterior wall of the abdomen, I penetrated it with the point of a large hypodermic syringe—shown in the wood-cut, Fig. 1; *a*, nozzle, *b*, body of instrument—and drew off a few drops of blood. This I submitted to microscopical examination, and found it to contain numerous masses of free pigment, irregular in form, and varying in size from the one one thousandth to the one three hundredth of an inch. I made several preparations of these masses, and they can be examined by those who are interested in the subject.

CASE II.—Mr. V. consulted me March 4th, 1875. In April, 1869, he walked on a hot day about half a mile, and on reaching his residence, feeling fatigued, lay down on a bed. He had scarcely done so, when he felt a tingling sensation in the right foot, and this gradually extended to the head. The next morning, on attempting to get into a carriage, he was seized with vertigo, and had to lie down. His physician prescribed *nux vomica*, and after a short time, being relieved, he traveled, and eventually recovered his usual health.

Five years afterward, while walking in the open air on a wet day, he had another attack on the right side, similar in all respects to that with which he had previously suffered, and accompanied with great dizziness. He immediately consulted a physician, who advised mountain air.

No further attack ensued till the early part of the present year. There were then similar symptoms, except as regarded vertigo, which was absent; but there was greater weakness

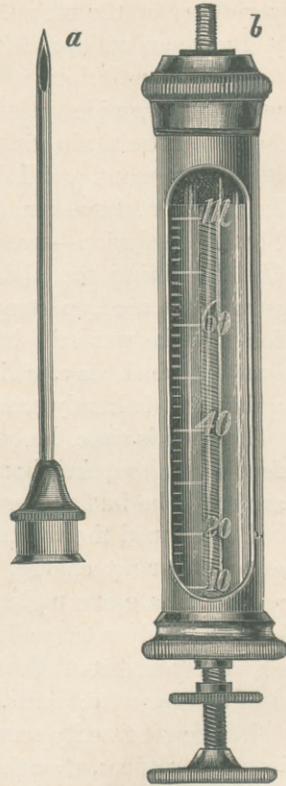


Fig. 1.

afterward, and some difficulty of articulation. During the past five years, the eyesight had been seriously impaired, and was entirely lost for a time, after protracted reading in the summer of 1874.

Before examining this patient, I found that he had pain in the head, frequent attacks of vertigo, great impairment of sight, and decided loss of mobility on the right side of the body. I further ascertained that he had suffered exceedingly from malarial fever, and that there was even then enlargement and induration of the spleen.

Upon examining the fundus of the eyes with the ophthalmoscope, I found double optic neuritis worse on the left side

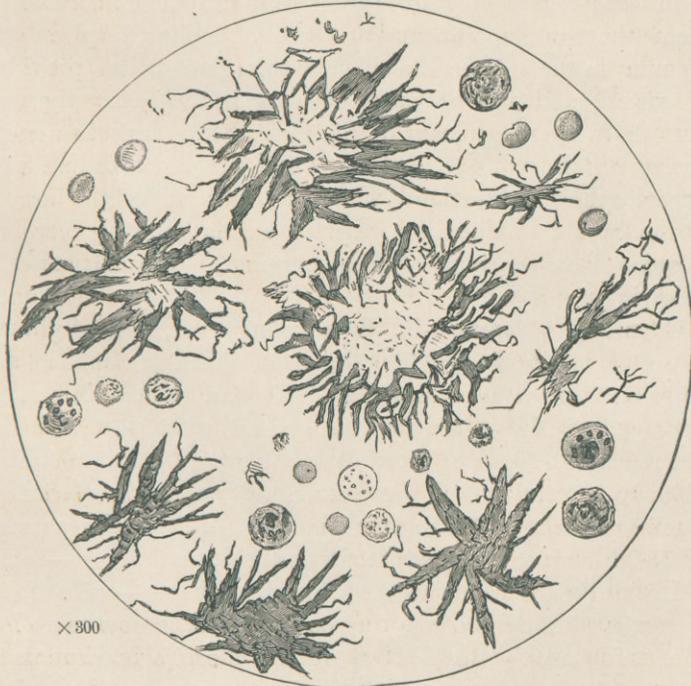


Fig. 2.

than the right, and large deposits of pigment in both retinae, especially the left. These masses were stellate in form, and followed, mainly, the course of the arterial branches. I then, as in the previous case, punctured the spleen, and drew off a

few drops of blood. Examined by the microscope, it was found to contain a large quantity of free pigment, as well as numerous pigment-holding cells. The free masses were of very remarkable form, and are well shown in the accompanying drawing made from the microscope with the camera lucida.

My friend, Prof. Roosa, examined this patient very carefully, and confirmed my view relative to the ophthalmoscopic appearances.

In several other cases in which there were cerebral symptoms, associated with pigmentary deposits in the fundus of the eye, there has been the history of repeated attacks of intermittent fever; and although I have not demonstrated in them the contemporaneous presence of enlarged spleen and pigment in the splenic blood, such enlargement has previously existed, and has probably been associated with pigment. And there are many cases of diseases of the nervous system, almost certainly due to malaria, which are accompanied with hypertrophied spleen, and which recover under the use of anti-malarial remedies, in which there is probably cerebral disorder from the deposition of pigment. Of such were the following:

CASE III. *Chorea*.—A. L., a young man, aged eighteen, consulted me in May, 1873, for chorea, affecting the face and limbs on both sides of the body. He had resided in a malarious part of New-York City for several years past, and had had repeated attacks of intermittent fever. In the summer of 1869, he had traveled in the Gulf States and had experienced renewed attacks of his former malady. During the autumn of 1872, he had repeated vertiginous seizures, almost—so far as I could judge from his description of them—epileptic in character, although he was very positive that there was no loss of consciousness. Soon afterward, the choreiform movements began. At first they were confined to the muscles of the right side of the face, then the left side was affected; next, the sterno-cleido-mastoidei and other muscles of the neck became involved, and then the arms and legs. When I saw him, the chorea had lasted about six months.

On examining the eyes with the ophthalmoscope, I found

numerous deposits of pigment, stellate in form, along the course of the arterial branches on both sides.

The spleen was enlarged to nearly double its natural size.

As the patient objected to my puncturing the spleen for the purpose of obtaining a specimen of its blood, I was unable to examine into the question of its containing pigment.

I treated him with arsenic, and in a month he was free from choreic symptoms. The pigmentary deposits in the retina remained during the whole time that he was under my observation, but caused no inconvenience to sight.

CASE IV. *Hypochondria*.—I. S., a lawyer, aged forty, came under my care in August, 1874. He had slight pain in the head, and was depressed mentally to such an extent that he had once attempted suicide.

He had three years previously, while residing on the eastern shore of Maryland, suffered from repeated seizures of intermittent fever, attended with enlargement of the spleen. The attacks, though arrested for a time by quinine, returned again and again. On one occasion, he had experienced an epileptiform paroxysm in the interval between the febrile exacerbations, and had suffered with his head ever since.

When I saw him, he was cachectic, his spleen was hypertrophied, he complained of numbness in various parts of the body, and he was not able to sleep well, though there was no marked insomnia.

I punctured the spleen and drew off a small quantity of blood. It contained both masses of free pigment and pigment-holding cells.

There were no abnormal ophthalmoscopic appearances beyond choked disk on both sides.

I treated him with the arsenious acid, $\frac{1}{25}$ grain, in pill, three times a day, and in a few days amendment began. He recovered perfectly in six weeks, and has remained well since.

CASE V. *Intermittent Aphonia*.—A. N., a young lady, aged nineteen, consulted me March 20th, 1875, for a loss of voice, supposed to be hysterical in character. She had for three years past experienced, every spring and autumn, attacks of intermittent fever, which were cut short by the use of quinine in large doses. The spleen had been very much en-

large, but had become somewhat reduced in size under the use of quinine, and when I saw her, was only slightly hypertrophied.

Further inquiry revealed the fact that the aphonia was intermittent, coming on regularly every alternate day at about ten o'clock, and lasting till late in the afternoon. There was neither chill nor fever. The splenic blood was not examined, owing to her objections, and there were no pigmentary deposits in the eyes, nor other abnormal conditions.

Under the use of arsenic, the aphonia was entirely relieved in a week, and a continuance of the remedy still further reduced the size of the spleen.

Although it has no direct relation with the subject of this paper, I may state that in Cases II. and IV., I employed the fluid extract of ergot in the treatment of the enlarged spleens, and by injecting it in drachm doses, directly into the organ, with the syringe figured. The effect was exceedingly well marked in causing rapid and permanent reduction in size. Six injections were used in Case II., and four in Case IV.

My views in relation to the connection between the deposits and the spleen are that the pigment is first formed in the spleen; that it enters the general circulation, is deposited in the bloodvessels of the brain, or passes through their coats, giving rise to disturbances in the functions of this organ; that it also often enters the ophthalmic vessels, and can be detected by ophthalmoscopic examination. Of course I do not mean to be understood as claiming that all pigmentary deposits in the retina and choroid have this origin; but it is scarcely a matter for doubt, in view of what I have brought forward, that they may be due to the cause in question. Writers upon ophthalmic pathology do not appear to have settled to their satisfaction the etiology of the retinal pigmentation. In some cases, it is certainly congenital, and seems to be of the nature of a true degeneration. Leber* denies that every case of pigmented retina is a true retinitis, and Wecker and Jaeger † indorse this opinion in very emphatic language. In the presence, however, of the eminent ophthalmologists who belong to this Association, it would be presumption for me to

* Archiv für Ophthalmologie, B. xv. S. 1.

† Traité des maladies du fond de l'œil, Paris, 1870, p. 134.

dwell upon this part of the subject. I will only say that no author, to my knowledge, suggests the splenic origin of the pigment in any case, although several call attention to the fact that the deposit is most marked in the course of the retinal vessels, and Stellwag expresses the view that it is the result of disease of the coats of the vessels. The possibility of pigment reaching the ocular vessels from the spleen will scarcely be questioned, inasmuch as the fact of embolism of the arteria centralis retinae, and of its branches, is established beyond a doubt by the investigations of Virchow, Von Graefe, Schweigger, Sichel, and others.

In order, however, to throw additional light on the subject, I instituted a series of experiments on dogs and rabbits, in which I injected finely-powdered indigo into the circulation, and which led to the demonstration of the possibility of the passage of the pigment into the retinal vessels. These are, however, not yet concluded, and I therefore do not dwell upon them at this time.

These experiments seem to show very conclusively that there is nothing impossible in the views brought forward. And from a consideration of the whole subject, I think we are warranted in concluding :

1st. That as a consequence of malarial poisoning, the pigment of the blood undergoes a change in appearance and form, and that the alteration is effected in the spleen, leading to hypertrophy of this organ.

2d. That this pigment may enter the general circulation from the spleen, either in a free condition or in pigment-holding cells, and that it may be deposited in the cerebral blood-vessels, or pass through their coats.

3d. That these deposits may give rise to various symptoms, indicating derangement of the nervous system.

4th. That arsenic appears to have the power of, in a way at present unknown, so altering the character of the pigmentary deposits as to facilitate their removal, and to cause the disappearance of the symptoms to which they give rise.

5th. That we may have, during the life of the individual, ocular demonstration of these facts by the presence of pigment in the fundus of the eye, as revealed by the ophthalmoscope.

Jan 10, 178